

B3 administering to a subject in need of such treatment an agent that down-regulates EDG receptor signaling in an amount effective to increase arterial blood flow.

B4 56. A method for inhibiting vasoconstriction in a subject who would benefit from inhibited vasoconstriction, comprising:

administering to a subject in need of such treatment an agent that down-regulates EDG receptor signaling in an amount effective to inhibit vasoconstriction.

B1.125 86
87. (New) The method of claim 34, wherein the agent is a sphingosine kinase inhibitor.

Sub C 87
88. (New) The method of claim 87, wherein the sphingosine kinase inhibitor is selected from the group consisting of methylsphingosine, N,N-dimethylsphingosine, trimethylsphingosine, D,L-threo-dihydrosphingosine, high density lipoprotein, and 3-fluoro-sphingosine analogues.

B1 88
89. (New) The method of claim 34, wherein the agent is an EDG receptor inhibitor.

89
90. (New) The method of claim 89, wherein the EDG receptor inhibitor is selected from the group consisting of EDG-1 receptor inhibitor, EDG-3 receptor inhibitor, EDG-5 receptor inhibitor, and EDG-8 receptor inhibitor.

90
91. (New) The method of claim 89, wherein the EDG receptor inhibitor is an EDG-3 receptor inhibitor.

91
92. (New) The method of claim 89, wherein the EDG receptor inhibitor is sphingosine or suramin.

92
93. (New) The method of claim 34, wherein the agent is a sphingosine-1-phosphate phosphatase activator.

~~93~~
~~94.~~ (New) The method of claim 34, wherein the disorder is selected from the group consisting of stroke, subarachnoid hemorrhage and cerebral vasospasm.

~~94~~
~~95.~~ (New) The method of claim 43, wherein the agent is a sphingosine kinase inhibitor.

~~95~~
~~96.~~ (New) The method of claim 95, wherein the sphingosine kinase inhibitor is selected from the group consisting of methylsphingosine, N,N-dimethylsphingosine, trimethylsphingosine, D,L-threo-dihydrosphingosine, high density lipoprotein, and 3-fluoro-sphingosine analogues.

~~96~~
~~97.~~ (New) The method of claim 43, wherein the agent is an EDG receptor inhibitor.

~~97~~
~~98.~~ (New) The method of claim 97, wherein the EDG receptor inhibitor is selected from the group consisting of EDG-1 receptor inhibitor, EDG-3 receptor inhibitor, EDG-5 receptor inhibitor and EDG-8 receptor inhibitor.

~~98~~
~~99.~~ (New) The method of claim 97, wherein the EDG receptor inhibitor is an EDG-3 receptor inhibitor.

~~99~~
~~100.~~ (New) The method of claim 97, wherein the EDG receptor inhibitor is sphingosine or suramin.

~~100~~
~~101.~~ (New) The method of claim 43, wherein the in agent is a sphingosine-1-phosphate phosphatase activator.

~~101~~
~~102.~~ (New) The method of claim 43, wherein the subject is having, or is at risk of having, a stroke, a subarachnoid hemorrhage or a cerebral vasospasm.

102

103. (New) The method of claim 43, wherein the arterial blood flow is cerebral artery blood flow.

103

104. (New) The method of claim 43, further comprising co-administering a second agent to the subject with a condition treatable by the second agent in an amount effective to treat the condition, whereby the delivery of the second agent to a tissue of the subject is enhanced as a result of the increased arterial blood flow.

104

105. (New) The method of claim 104, wherein the second agent is selected from the group consisting of analeptic, analgesic, anesthetic, adrenergic agent, anti-adrenergic agent, amino acids, antagonists, antidote, anti-anxiety agent, anti-cholinergic, anti-convulsant, anti-depressant, anti-emetic, anti-epileptic, anti-hypertensive, anti-fibrinolytic, anti-hyperlipidemia, anti-migraine, anti-nauseant, anti-neoplastic (brain cancer), anti-obsessional agent, anti-obesity agent, anti-parkinsonian, anti-psychotic, appetite suppressant, blood glucose regulator, cognition adjuvant, cognition enhancer, dopaminergic agent, emetic, free oxygen radical scavenger, glucocorticoid, hypocholesterolemic, hypolipidemic, histamine H2 receptor antagonists, immunosuppressant, inhibitor, memory adjuvant, mental performance enhancer, mood regulator, mydriatic, neuromuscular blocking agent, neuroprotective, NMDA antagonist, post-stroke and post-head trauma treatment, psychotropic, sedative, sedative-hypnotic, serotonin inhibitor, tranquilizer, and treatment of cerebral ischemia, calcium channel blockers, free radical scavengers - antioxidants, GABA agonists, glutamate antagonists, AMPA antagonists, kainate antagonists, competitive and non-competitive NMDA antagonists, growth factors, opioid antagonists, phosphatidylcholine precursors, serotonin agonists, sodium- and calcium-channel blockers, and potassium channel openers.

105

106. (New) The method of claim 104, wherein the second agent is TPA.

~~106~~
~~107.~~ (New) The method of claim 56, wherein the agent is a sphingosine kinase inhibitor.

~~107~~
~~108.~~ (New) The method of claim 107, wherein the sphingosine kinase inhibitor is selected from the group consisting of methylsphingosine, N,N-dimethylsphingosine, trimethylsphingosine, D,L-threo-dihydrosphingosine, high density lipoprotein, and 3-fluoro-sphingosine analogues.

~~108~~
~~109.~~ (New) The method of claim 56, wherein the agent is an EDG receptor inhibitor.

~~109~~
~~110.~~ (New) The method of claim 109, wherein the EDG receptor inhibitor is selected from the group consisting of EDG-1 receptor inhibitor, EDG-3 receptor inhibitor, EDG-5 receptor inhibitor and EDG-8 receptor inhibitor.

~~110~~
~~111.~~ (New) The method of claim 109, wherein the EDG receptor inhibitor is an EDG-3 receptor inhibitor.

~~111~~
~~112.~~ (New) The method of claim 109, wherein the EDG receptor inhibitor is sphingosine or suramin.

~~112~~
~~113.~~ (New) The method of claim 56, wherein the agent is a sphingosine-1-phosphate phosphatase activator.

~~113~~
~~114.~~ (New) The method of claim 56, wherein the subject is having or is at risk of having a stroke, a subarachnoid hemorrhage or a cerebral vasospasm.

~~114~~
~~115.~~ (New) The method of claim 56, wherein the vasoconstriction is cerebral vasoconstriction.

Serial No.: 09/804,987

- 6 -

Art Unit: 1646

Respectfully Submitted,



Maria A. Trevisan, Reg. No. 48,207
Wolf, Greenfield & Sacks, P.C.
Federal Reserve Plaza, 600 Atlantic Avenue
Boston, MA 02210-2211
Attorney for Applicants

Docket No. M00765/70035 (ERG/MAT)

Date: August 14, 2002

x08/16/02